REMARKS

The Amendment, filed in response to the Office Action mailed November 18, 2009, is believed to fully address all and every issue raised in the Office Action. Favorable reconsideration on the merits and allowance of the application are respectfully requested.

Applicant thanks the Examiner for withdrawing previous rejections.

Claims Disposition and Summary of Amendment

In the November 18, 2009 Office Action, claims 11 and 20-28, 35, and 36 have been considered and rejected. Claims 29-34 were withdrawn from consideration as being drawn to non-elected subject matter.

In the instant Amendment, claims 11 and 20-34 are canceled without prejudice or disclaimer.

In the instant Amendment, claims 35 and 36 are amended in order to more clearly set forth the claimed subject matter, in particular by further defining

(a) the kind of the cartilage-related disease and the active ingredient having an EP2 agonist activity to compound of (1-1) (in claim 35); and

(b) the substance having EP2 agonist activity to be limited to the compound represented by formula (1-1) (in claim 36).

New claims 37-42 are added. They are supported by original claims 22-26 and the disclosure at paragraph [0340] in the published application (Application Publication No. 20070270489).

Response to Rejection of Claims 11 and 20-26 under 35 U.S.C. §112, first paragraph

On page 3 of the Action, claims 11 and 20-26 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. In particular, the Examiner asserts that the amendment changing the transitional phrase from "comprising" to "consisting of" constitutes a new matter. Paragraph 6 of Office Action.

In response, without conceding the rejection, solely in order to advance the prosecution, Applicant cancels claims 11 and 20-26, rendering the rejection moot.

Applicant notes that claims 35 and 36 are not included in the 35 U.S.C. § 112, written description requirement rejection, while they recite "consisting of" administering a compound. In this juncture, Applicant respectfully submits the following arguments:

In asserting that the amendment changing the word "comprising" to "consisting of" introduces new matter, the Examiner appears to consider that the words "comprising" and "consisting of" are mutually exclusive; and that the specification provides embodiments of a method consisting of administering some embodiment of EP2 agonists, but not representative embodiments of the whole scope of EP2 agonists.

"Consisting Of"

Applicant disagrees with the Examiner's position and interpretation of the term "comprising" used in the specification.

The word "comprising" is a term of art used in claim language which means that the named elements are essential, but other elements *may be added* and still form a construct within the scope of the claim. Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986) (Emphasis added by Applicant). That is, the term "comprise" does not require that the claimed subject matter include additional unspecified components. Such inclusion is

merely optional. Therefore, the phrase "comprising" encompasses two possible embodiments: (1) an embodiment which includes only those particular components recited in the claim, and (2) an embodiment which includes those particular components recited in the claim and the inclusion of other unspecified components.

Applying this interpretation to the instant application, the original claim language "comprising" encompasses (1) "consisting of a substance having an EP2 agonist activity" and (2) further optional inclusion of unspecified ingredients such as medicaments for treating other bone diseases.

Such interpretation is consistent with the Applicant's intent which is clearly shown in the disclosure of the specification, where Applicant states "the remedy of the present invention may be administered as a combined preparation, and especially may be used with medicaments for treating other bone diseases." Page 63 of the present specification. This description is crystal clear that "the remedy may be used with other medicaments," but *not* "*must* be used with other medicaments." That is, Applicant conceived an administration of the claimed compound alone as an active ingredient, and in addition, an administration of the claimed compound in combination with other medicaments

Furthermore, Formulation Examples 1-4 on page 73 of the specification describe embodiments of the claimed composition consisting of an EP2 agonist as the only active ingredient, thereby providing clear support for the "consisting of" transitional phrase in the claims. In this regard, Applicant notes that the Examiner concedes the specification describes embodiments of a method consisting of administering a compound of formula (I-1).

Support for whole scope of Compound (I-1)

The specification discloses that the present inventors have found that the expression of EP2 and EP3 is located at epiphysial cartilage. Moreover, as a result of large variety of functional analysis in chondrocyte or cartilage, the present inventors have found that EP2 and EP3 agonists have an effect of stimulating chondrogenesis. (See page 3, lines 25-29). Furthermore, Figures 4, 7 and 8 of the instant application clearly demonstrate the correlation between EP2 agonist activity and stimulating chondrogenesis, and therefore the specification provides support for a reasonable correlation between EP2 agonist activity and stimulating chondrocyte growth.

Nevertheless, Applicant, for the interest of advancing the prosecution, amends claim 35 and 36 to recite a method consisting of administering a compound of formula (I-1) to treat certain kinds of diseases.

Response to Claim Rejections under 35 U.S.C. § 103

On page 4 of the Action, claims 11 and 20-25 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Cameron *et al* (WO 98/27976) ("Cameron"), alone or further in view of Anastassiades (US Patent 6,133,230).

On page 4 of the Action, claim 26 is rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Cameron (WO 98/27976), alone or further in view of Anastassiades (US Patent 6,133,230) as applied to claims 11 and 20-25 above, and optionally further in view of Fortier et al (J. Bone Joint Surg., Vol. 84-B, pp. 276-288, 2002; previously cited).

On page 8 of the Action, claims 27, 28, 35, and 36 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Cameron (WO 98/27976), alone or further in view of

Anastassiades (US Patent 6,133,230) as applied to claims 11 and 20-25 above, and further in view of Tani *et al* (US Patent 6,110,969) ("Tani").

Regarding claims 11 and 20-26

In response, without conceding the rejections, solely in order to advance the prosecution, Applicant cancels claims 11 and 20-26, rendering the rejections of claims 11 and 20-26 moot.

Regarding claims 35 and 36, and new claims 37-42

With respect to claims 35 and 36, Applicant respectfully submits that, as discussed above, claims 35 and 36 are amended to cancel diseases which are disclosed in Cameron and to limit the scope of EP2 agonist compounds to the compounds of formula (I-1). Based on currently amended claims 35 and 36, Applicant traverses the rejection for the following reasons.

(1) None of Cameron, Anastassiades, or Tani fails to teach or suggest the effect of inhibiting cartilage calcification. Cameron and Tani relate to *bone diseases*, rather than cartilage diseases, and Anastassiades does not describe EP2 agonist. And, the combined teachings of Cameron, Anastassiades, and Tani does not teach all and every limitation of currently amended claims 35 and 36.

(2) There is no motivation or guidance to combine the teachings of Cameron with Anastassiades, and Tani, because Cameron teaches away from the claimed invention by teaching increasing bone mass and cartilage diseases (recited in claims 35 and 36) become worse or more serious when cartilage is ossified (i.e., if bone mass is increases).

(3) There is no reasonable expectation of success or predictability of success to reach the claimed invention, by modifying the combined teachings of Cameron, Anastassiades, and Tani, because cartilage is different from bone, and cartilage diseases (recited in amended claims 35 and 36) cannot be treated by increasing bone mass (as taught by Cameron).

(4) Therefore, the present invention (in particular the effect of inhibiting cartilage calcification) cannot easily be reached from the disclosures of Cameron WO 98/27976, Anastassiades '230, and Tani '969, either alone or in their combinations.

Applicant discusses each of the above points in more detail below.

The currently amended claim 35 recites "rheumatoid arthritis, osteoarthritis, cartilage damage, articular disk damage, meniscus injury, chondrodysplasia, achondroplasia, achondrogenesis, dyschondrogenesis, chondrodystrophia, articular chondrocalcinosis, acute purulent arthritis, tuberculous arthritis, syphilitic arthritis, systemic lupus erythematosus, spondylosis deformans, disk herniation, injury by sports and keypuncher's disease."

These diseases are all related to cartilage damage and are totally different from the condition which presents with low bone mass or skeletal disorders of Cameron. In the present application, the compound of general formula (I-1) stimulates chondrogenesis, inhibits the calcification of cartilage by inhibiting osteopontin expression and thus treats the above diseases.

The present invention is for the maintenance of the flexibility and viscoelasticity of cartilage by stimulating chondrogenesis and further inhibiting cartilage calcification. This function or effects cannot be obtained by bone formation or bone mass increase as described in Cameron for the reasons described below. As such, one skilled in the art would not have been motivated to modify the teachings of Cameron to reach the claimed invention, with reasonable expectation of success or reasonable predictability.

Bone is a very rigid tissue and protects internal organs as well as serves as a rigid structure to the human body. On the other hand, cartilage, which covers the ends of bone, is a smooth, tough, resilient, and protective tissue composed of collagen, water, and proteoglycans. And cartilage has a role to reduce friction among bones as a joint moves, which is different from

the role of bone. See, The Merck Manual of Medical Information-Bones and Joints. A copy of the relevant pages of the Merck Manual are attached as Exhibit A and Exhibit B. In this regard, Applicant respectfully submits that it is not required to submit an IDS for submitting these documents for Examiner's consideration, because these and the other attached documents are submitted in support of Applicant's arguments that are made in response to the Examiner's rejection. MPEP 609.05.

Referring to the Exhibits A and B, in a joint, cartilage at the ends of bone plays a role like a cushion for bone, and its flexibility and viscoelasticity are the functions specific to cartilage. Thus, the damage or hardening of cartilage leads to the loss of flexibility and viscoelasticity which are a characteristic of cartilage and become a cause of the cartilage-related diseases cited in the amended claims.

For example, hardening of subchondral bone, osteophyte formation and the like are observed in osteoarthritis accompanying the change in which cartilage viscoelasticity is lost by metabolic abnormality of cartilage matrix. See, The Merck Manual of Medical Information regarding "Osteoarthritis." A copy of the relevant parts of The Merck Manual is attached as Exhibit C. Also, it is known that osteophyte is formed when marginal bone of a joint overgrows. See, Clinical Calcium, Vol.18, No.11, English Abstract (Exhibit D).

In addition, for example, as described at lines 4-15 on page 9 of the present specification, articular chondrocalcinosis is a typical disease caused by abnormality in cartilage calcification, and the calcification of cartilage leads to the loss of cartilage flexibility and to the loss of its function.

The above diseases accompanied by cartilage disorder cannot be treated by increasing bone mass. In the treatment of the above diseases, it is of course necessary to stimulate

chondrogenesis. In addition, it is also necessary to maintain cartilage flexibility by inhibiting the calcification and hardening of cartilage and to maintain its function as cartilage in order to bend and extend a joint.

On the other hand, in Cameron, EP2 agonist increases bone mass and treats the condition of low bone mass, such as osteoporosis or bone fracture. The above diseases in the amended claims 35 and 36 of the present application are not conditions of low bone mass and thus cannot be treated by increasing bone mass. Also, Cameron describes the bone formation, but does not describe cartilage formation, much less describe or mention the effect of inhibiting cartilage calcification.

Applicant notes that the Examiner asserts that "Cameron et al do teach that the mammal to be treated may present with low bone mass or other skeletal disorders and that the compound used may be applied to the cartilage growth plate, and therefore one skilled in the art would reasonably expect that the subject would be in need of stimulating chondrocyte growth in order to form new bone tissue" at lines 15-19 on page 5 (paragraph 8) of the Office Action. However, the applicants believe that one skilled in the art **would not be able to reasonably predict the recited function** (stimulating chondrogenesis) at the administration locus (the cartilage growth plate) for the reasons as presented above and supported by technical references. Further, the diseases recited in amended claims 35 and 36 of the present application are not treated by bone formulation, and it is predicted that the above diseases rather deteriorate when new bone is formulated, that is, ossification of cartilage is promoted and the cartilage flexibility is lost.

Therefore, Applicant respectfully submits that one skilled in the art would not have motivated or guided to reach to the idea of cartilage formation and effect of inhibiting cartilage calcification of the present invention from the disclosure of Cameron. Instead, **Cameron**

teaches away from the present invention because the deterioration of cartilage functions and deterioration of the above diseases by cartilage hardening are predicted.

Anastassiades describes the effect of stimulating chondrogenesis of PGE1. However, Anastassiades does not describe the EP2 agonist or the condition of low bone mass described in Cameron. Therefore, Applicant submits that there is no ground for combining Cameron and Anastassiades. Also, the Examiner fails to provide any rationale or scientific reasoning as to why one skilled in the art would have been motivated to combine these two references to reach the claimed invention, with reasonable expectation or predictability of success.

In addition, Anastassiades does not describe or mention the compound of formula (I-1) or effect of inhibiting cartilage calcification. Thus, Applicant believes that one skilled in the art cannot easily reach to the idea that the compound of formula (I-1) inhibits cartilage calcification and treats the above cartilage-related diseases as well as stimulates chondrocyte.

Tani describes that the compound of formula (I-1) as an EP2 agonist is effective for osteodystrophy. However, in Tani, there is no description related to cartilage formation or effect of inhibiting cartilage calcification at all. The Examiner asserts that "One would reasonably expect success from the use of the species of Tani et al with the method of Cameron et al because both references are drawn to treatment of abnormal bone formation using a substance having EP2 agonist activity" in the Office Action. However, as discussed above, the bone diseases described in Cameron and Tani are different from the cartilage diseases recited in amended claims 35 and 36, and the diseases recited in amended claims 35 and 36 cannot be treated by increasing bone mass. Therefore, Applicant respectfully submits that combined teachings of Cameron and Tani fails to teach all and every element of amended claims 35 and 36.

In sum, the combined teachings of Cameron, Anastassiades, and Tani fail to teach all and every elements of amended claims 35 and 36; and Cameron teaches away from the subject matter of amended claims 35 and 36.

With respect to new claims 37-42, Applicant respectfully submit that these claims should be allowable because they directly or indirectly depend from claims 35 or 36 and thus are allowable for the same reasons of patentability of amended claims 35 and 36.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number **202-775-7588**.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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CUSTOMER NUMBER

Attachments: Exhibits A - D (under separate cover)